

DETAILED ACTION

This office action is in response to applicant's reply filed on May 2, 2008.

Status of Claims

Claims 1-4, 6-8, 13-20, 22-67 and 136-140 are currently pending and are the subject of this office action.

Claims 2-4, 6-8, 13-15, 19-20, 22-54, 56, 59-67, 136-137 and 140 were withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions/species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on November 1, 2007.

Claims 1, 16-18, 55, 57-58, and 138-139 are currently under examination.

Priority

This application is a 371 of PCT/IL05/00149 filed on 02/06/2005, which claims benefit of Provisional Application No. 60/541,904 filed on 02/06/2004.

References

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but

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must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Response to Arguments

This is in response to applicant's arguments, filed on May 2, 2008.

Claims rejected under 35 USC 112, first paragraph (enablement).

Applicant's arguments have been fully considered but are not persuasive.

Applicant stated: "If the idea is that experiments in humans have to be presented or at least be shown to exist in the art for related compounds, this is a requirement beyond what the law requires and beyond the authority of the PTO. The examiner is not authorized to act on behalf of the FDA, and has no authority to require that clinical trials must be conducted and used as evidence to provide enablement for method of treatment claims (see page 5 of the May 2, 2008 response)." Examiner completely agrees with this statement. At no point in the enablement rejection a clinical trial or human data was requested. The Examiner was making the case that there are sufficient reasons, based on the prior art and on applicant's own specification, to believe that one skilled in the art will not be enabled to use the claimed invention (treatment of melanoma with compound 106) without undue experimentation and that applicant has not presented enough evidence in order to enable the present application. At no point was suggested or requested that applicant should present human clinical data for this application to overcome the enablement rejection. Other *in vitro* or *in vivo* assays will

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suffice, but the data presented by applicant does not suffice to overcome the enablement rejection (see discussion below).

A conclusion of lack of enablement means that, based on the evidence regarding each of the *Wands* factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (see MPEP 2164.01(a)). Also, the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The “amount of guidance or direction” refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (see MPEP 2164.03).

Despite all the examples that Applicant mentions in pages 14-17 of the May 2, 2008 response, regarding small molecule inhibitors of heparanase, and despite all the knowledge and advances in understanding the biology and implications of inhibiting heparanase activity, the following statement regarding

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the state of the prior art, already mentioned in the Office Action mailed on 12/04/07, regarding small molecule heparanase inhibitors, remains true: there are no examples of small molecule heparanase inhibitors in the prior art for any of the following cases: 1- correlation of the *in vitro* inhibition of heparanase and efficacy in humans, 2- there are very few examples correlating *in vitro* inhibition of heparanase and efficacy in animals, and 3- there are no examples of correlation between efficacy in animal models and efficacy in humans. The only molecule that shows correlation between enzyme inhibition, animal models and human data is PI-88 (a highly sulfonated oligosaccharide) which is believed not to be a selective heparanase inhibitor (see discussion below), so there are still doubts regarding what causes its *in vivo* activity (see discussion below). In fact, one of the references mentioned in pages 14-17 of the May 2 response: Pan et. al. (Biorg. Med Letters (2006) 16:409-412, which it is mentioned in the McKenzie review, contrary of what applicant stated in the May 2 response) mentions that only recently, small molecule heparanase inhibitors were reported (see page 409, end of first paragraph) and that a need of proof was needed (see start of second paragraph) meaning that there is still a need to find a small heparanase inhibitor which is selective in order to make a direct correlation between heparanase inhibitory activity and biological activity. The reference, even though provides *in vitro* and *in vivo* data, fails to give a selectivity profile for the disclosed compounds, so the question of validation still remains unanswered. In fact the manuscript concludes with the following statement: "active effort is in progress to further prove the link between the inhibition of heparanase activity and efficacy

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observed in the B-16 (melanoma *in vivo* study), and the results will be reported in due course”.

This demonstrates that there is still no clear validation regarding heparanase inhibition by small molecules and biological activity. There is evidence to suspect about the biological consequences of inhibiting heparanase activity with small selective molecules, but still no clear evidence. So, as it was mentioned before, the enablement requirements depend on the knowledge of the prior art: the more is known the less information is required, inversely, the less is known the more data is required. In the case of heparanase inhibitors, since there is no clear correlation between *in vitro* enzyme inhibition and *in vivo* efficacy in the treatment of melanoma, there is a need for some cellular or animal data for enablement. In the instant case the only data provided for the elected compound (106) is the *in vitro* enzyme inhibition. There is no data provided for compound 106 for the cell invasion assay described in page 67 of the specification (see Table on Appendix A of the specification) or in an angiogenesis assay. There is also no data in the *in vitro* B16-BL6 melanoma cell assay and/or in an *in vivo* B16-BL6 melanoma tail vein model, which are assays universally accepted as predictors for the efficacy in the treatment of melanoma in humans. So based on the data provided in the specification (only heparanase enzyme inhibition for compound 106) and based on the state of the prior art (no definitive correlation between inhibition of heparanase enzyme by small molecules and treatment of melanoma), it is concluded that the skilled in the art would have to engage in undue experimentation with no assurance of success, for example the

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compound would have to be tested in an angiogenesis assay (see for example US patent 7,138,425, also mentioned by applicant on page 15 of the May 2 response, where a patent was granted on small molecule inhibitors of heparanase based on inhibition of the heparanase enzyme and the angiogenesis assay) and/or and in vitro B16-BL6 melanoma cell assay and/or in an *in vivo* B16-BL6 melanoma tail vein model, and then if efficacy is observed in the *in vivo* model, determine a dose response curve and extrapolate a dosage for human treatment. All this is undue experimentation. In summary, even though human data is definitively not required for enablement, there is still a minimum of information that applicant has to provide based on the knowledge of the prior art in order to enable the invention, and based on the prior discussion, applicant has not met that criteria for the specific case of treating melanoma with compound 106.

Applicant mentions, after several prior art references are cited, that the rejection is clearly wrong in alleging that the prior art does not disclose small molecules as heparanase inhibitors (last three lines of page 22 of the May 2 response). At no point the rejection mentions that the prior art does not disclose small molecules as heparanase inhibitors, what the rejection mentions is that there are very few small molecules available as heparanase inhibitors, and very few have animal data associated with it, and none is in clinical trials (see office action mailed on December 4, 2007, page 6, last 4 lines), which is corroborated by the McKenzie review and by some of the references cited by applicant that were discussed above.

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Regarding the comments of Dr. Joel M. Van Gelder (page 23 of the May 2 response) regarding the differences between small molecules and PI-88 (a sulfated oligosaccharide and so far the only heparanase inhibitor in clinical trials) one has to be very careful in making a direct correlation between the inhibition of heparanase *in vitro* and its *in vivo* effect in animals, since this compound is multifunctional, potentially complicating an understanding of its mode of action (see Courtney et. al., page 3269, right column, first paragraph). Also McKenzie mentions that PI-88 has a dual mode of action, inhibiting heparanase and interfering with the binding or action of HS-bound growth factors (see page 7, last line of left column until line 3 of right column). In other words, PI-88, although effective in animals is not a selective heparanase inhibitor, so its *in vivo* activity might be due to other factors not related or partially related to heparanase activity. Also, nobody denies the common pharmacophore of the compounds of the instant application and the ones in the prior art, but the art is full of cases of compounds with similar pharmacophores with completely different biological activity.

Dr Van Gelder also mentions that "it is not easy to find a correlation between inhibition of invasion *in vitro* and an anti-metastatic effect *in-vivo* since only a few *in vivo* metastasis models and anti-metastatic agents exists". This is true; however, as discussed above, there are other *in vitro* or *in vivo* assays that correlate very well with the treatment of melanoma in humans that were not provided in the instant application.

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In conclusion, even though it is obvious that applicant has discovered new heparanase inhibitors, it does not provide enough evidence, as discussed above, in order to enable treating melanoma with compound 106.

Rejection under 35 USC 112 (enablement) is maintained.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 16-18, 55, 57-58, and 138-139 are rejected under 35 U.S.C.

112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561

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(Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the

Federal Circuit has stated that:

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. *PPG v. Guardian*, 75 F.3d 1558, 1564 (Fed. Cir. 1996). As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

- 1- the quantity of experimentation necessary,
- 2- the amount of direction or guidance provided,
- 3- the presence or absence of working examples,
- 4- the nature of the invention,
- 5- the state of the prior art,
- 6- the relative skill of those in the art,
- 7- the predictability of the art, and
- 8- the breadth of the claims

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

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1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to a method for treatment of a disease or disorder (melanoma is the species elected) caused by or associated with heparanase catalytic activity, said method comprising administering to a patient in need an effective amount of a heparanase inhibitor of the general formula **Id** (see claim 16, compound 106 is the species elected).

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

The factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies with the degree of unpredictability of the factors involved", and physiological activity is considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved); *Nationwide Chemical Corporation, et. al. v. Wright, et. al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances); *Ex parte Sudilovsky* 21 USPQ2d 1702 (Applicant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable); *In re Wright* 27 USPQ2d 1510

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(the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian vaccine was uncertain).

As illustrative of the state of the art for treating cancer in general, the examiner cites Gura et. al. (Science, 1997, 278:1041-1042, cited in previous office action), and Johnson et. al. (British Journal of Cancer, 2001, 84:1424-1431, cited in previous office action). Gura et. al., cited for evidentiary purposes, teaches that researches face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and further teach that since formal screening began in 1955, many thousand of drugs have shown activity in either cell or animal models, but only 39 have actually been shown useful for chemotherapy (see page 1041, first and second paragraph). Also, with regard to unpredictability, Johnson et al., also cited for evidentiary purposes, teach that the in vivo activity of 39 different agents in a particular histology in a tumor model did not correlate to activity in the same human cancer (see Results on page 1426). *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Further, the mode of action of anticancer agents is often unknown or very unpredictable and administration of such agents is often accompanied by undesirable side effects.

Regarding more specifically to the treatment of different types of cancer with inhibitors of heparanase the examiner cites: Ishida et. al. (The Journal of Antibiotics, 2004, 57:136-142, cited in previous office action), Courtney et. al. (Bioorganic and Medicinal Letters, 2004, 14:3269-3273, cited in previous office

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action), and McKenzie (British Journal of Pharmacology, 2007, 151:1-14, cited in previous office action). Ishida et. al. teach that most heparanase inhibitors reported by now (February 2004) are derivatives of sulfated oligosaccharides similar to the substrate Heparan Sulfate, and not low molecular weight compounds (see page 136, column 2, second paragraph). Courtney et. al. also teach that even though Heparanase offers an attractive drug target, progress in this area has been limited by the current available repertoire of inhibitors. The most advanced inhibitor is PI-88 (a highly sulfonated mannan oligosaccharide), which is currently in Phase II clinical trials (and so far the only known heparanase inhibitor in clinical trials, see page 3269 first paragraph). So there are still no small molecule inhibitors of heparanase in human trials for the treatment of any type of cancer. In a recent review (2007), McKenzie shows that there are very few small molecules available as heparanase inhibitors, and only in one case they show animal data in a B16-B16 melanoma tail vein model (see page 7 under "Small molecule inhibitors: Imclone Systems Incorporated). They also mention, regarding another group of small molecule heparanase inhibitors, that unfortunately there is no published data on the efficacy of any of the small molecule inhibitors in animal studies, hence it remains to be seen whether these compounds will actually have efficacy *in vivo* (see page 7, first paragraph).

These articles plainly demonstrate that the art of developing and testing anticancer drugs, particularly for use in humans, is extremely unpredictable, particularly in the case of a single compound or genus of compounds being used to treat any and all cancers or different type of diseases. There are also no

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examples of small molecule heparanase inhibitors in the prior art for any of the following cases: 1- correlation of the *in vitro* inhibition of heparanase activity and efficacy in humans, 2- there are very few examples correlating *in vitro* inhibition of heparanase activity and efficacy in animals, and 3- there are no examples of correlation between efficacy in animal models and efficacy in humans.

2. The breadth of the claims

Even though the current examination is restricted to compound 106 and melanoma as the type of cancer to be treated, applicant should be aware that the claims vary in breadth; some (such as claims 1, 16, 17) vary broadly, reciting the treatment of broad genus of diseases with a broad genus of compounds. Others, such as claim 18 are narrower, reciting specific species of the claimed genus of compounds, but still claiming a broad genus of diseases.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification only provides *in vitro* heparanase inhibition data for compound 106. The specification also provides an *in vitro* assay of invasion inhibition by heparanase inhibitors, but no data for compound 106. There is no animal data to corroborate that these compounds will have efficacy in animals, even less in humans. The specification provides no direction or guidance for determining the particular administration regimens (e.g., dosages, timing, administration routes, etc) necessary to treat melanoma with compound 106.

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The directions concerning treating cancer (melanoma) are found in the specification at pages 41-44 and 64-68, which merely states Applicants' intention to do so by providing *in vitro*, *ex vivo* and *in vivo* assays, but compound 106 was not tested in any of those assays, except for the *in vitro* heparanase inhibition mentioned at the beginning of this paragraph.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept that instantly claimed compound 106 could be predictably used as treatment for melanoma. Since there is no precedent in the literature for the treatment of melanoma with any of the claimed compounds or similar compounds, how is the skilled physician supposed to know how to dose this compound in order to treat melanoma? Determining if the claimed compound 106 (or any of the non-elected compounds), would treat melanoma (or any particular cancerous disease) would require formulation into a dosage form, and subjecting into clinical trials or to testing in an assay known to correlate to clinical efficacy of such treatment. This is undue experimentation given the limited guidance and direction provided by Applicants.

Accordingly, the inventions of claims 1, 16-18, 55, 57-58, and 138-139 do not comply with the enablement requirement of 35 U.S.C 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the

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art would have to engage in undue experimentation with no assurance of success.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCOS SZNAIDMAN whose telephone number is (571)270-3498. The examiner can normally be reached on Monday through Thursday 8 AM to 6 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael P. Woodward can be reached on 571 272-8373.

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The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MARCOS SZNAIDMAN/
Examiner, Art Unit 1611
June 4, 2008

/MP WOODWARD/
Supervisory Patent Examiner, Art Unit 1615